REMARKS

Upon entry of this amendment, Claims 32-42 constitute the pending claims. These new claims are presented in order to more precisely define the subject matter claimed. These new claims are supported throughout the instant specification, including the original claims. Claims 3-6, 11, 30, and 31 are canceled without prejudice in view of the new Claims 32-42. Applicants reserve the right to prosecute claims of identical or similar scope in future applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. § 112, first paragraph – Written Description

Claims 3-6, 11, 30, and 31 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

The Office Action alleges that the specification does not provide adequate written description, *e.g.*, "sufficient structural information," (page 7 of the Office Action) for an "isolated human polypeptide" or an "isolated human pathogen polypeptide," nor adequate written description concerning "what amino acid residues are associated with a human polypeptide or human pathogen polypeptide." Applicants respectfully disagree.

Applicants submit that the claimed genus of human polypeptides or human pathogen polypeptides (hereafter "claimed polypeptide") are defined by both structural and functional terms, similar to the various polynucleotides in Example 9 of the "Revised Interim Written Description Guidelines Training Materials" (See comparison below). Applicants have adequately described the claimed genus by describing a representative number of species within the genus.

Specifically, the genus is defined by functional terms, *e.g.*, requiring the claimed polypeptide to: (1) bind PV- or MS-associated HLA-DR proteins, and (2) activate autoreactive T-cells, when bound to the respective HLA-DR proteins.

In addition, contrary to the Examiner's assertion, the genus is defined by structural terms: each claimed polypeptides is defined by a *sequence motif* that provides the structural restrictions

on such claimed polypeptides. Applicants submit that the Office Action seems to have mis-undertood certain disclosures of the specification, and that the specification provides sufficient structural information to satisfy the written description requirement.

First of all, the specification defines the term "sequence motif" on page 50:

> The term "sequence motif," in accordance with description provided herein, means a series of restrictions on the residues which may occupy certain relative positions of an amino acid sequence. A sequence motif must restrict at least three and preferably four or five positions of an amino acid sequence. The relative positions of the first (N-terminal) and last (C-terminal) restricted amino acid positions shall be separated by at least two but no more than twelve amino acid residues. For example. P1 and P4 may be the first and last restricted residues and these residues are separated by two residues. As another example, P-1 and P11 may be the first and last restricted residues and these are separated by ten residues. Positions between the first and last restricted positions may be restricted or unrestricted with the exception that a total of at least three positions of the motif must be restricted. Of the three positions which must be restricted, at least two must be residues corresponding to major MHC binding pockets. If only two of the restricted residues correspond to MHC binding residues, the third must correspond to a TCR contact residue. Further. at least one of the positions restricted must correspond to either the P1 or P4 binding position. By "restricted" is meant that at least one, and preferably ten, amino acid residues shall be excluded from a position.

This definition for "sequence motif" applies to the claimed sequence motifs for a PV- or MS-associated HLA-DR protein, and each sequence motif contains the core MHC binding residues.[1] This definition not only provides a detailed description, but also defined structural limitations on the claimed polypeptides.

Secondly, the claimed invention requires the subject HLA-DR proteins to be of the DR2 or DR4 subtype, and to be associated with either PV or MS. The specification further teaches that only specific HLA alleles are associated with PV or MS: PV is associated with one of many DR4 alleles (DRB1*0402) and a rare DQ1 allele (DQB1*05032) (p2, 1st full paragraph; p35, last paragraph). MS is associated with the most common DR2 subtype DRB1*1501 (p40, 1st paragraph) and DQ1 (p43, 1st full paragraph). Thus the claimed *PV- or MS-associated HLA-DR proteins*, including their known sequences, are adequately described in the specification or well-

[1] The "core MHC binding residues" are defined as "residues of an epitope corresponding to the P-1 to P9 positions of a peptide bound to an HLA-DR molecule." (see definition on page 52, last paragraph). "Sequence motif" is also clearly defined on page 50, first paragraph.

known at the time of filing.

Additionally, the specification describes in detail the general approach to derive sequence motifs for *any* disease-associated HLA alleles (p14-25). This includes HLA alleles associated with certain *unclaimed* autoimmune diseases.[2] There, the specification describes the pocket structures for each of the key *MHC contact residues of the sequence motif* (*e.g.*, P1, P4, P6, P7, and P9), with frequent reference to the Rheumatoid Arthritis (RA)-associated HLA alleles (see p14-18). The specification goes on to describe the general criteria for selecting the *TCR contact residues of the sequence motif* (*e.g.*, P-1, P2, P3, P5, P8, and P11). See p18-19. The whole general approach is then elaborated and summarized in pages 19-25.

Lastly, applying the general teachings about the sequence motifs described above, the specification describes in detail two specific examples relating to the PV and MS sequence motifs (p35-49), which are encompassed by the claims. In these example, PV motif #1 and MS motifs #1-3 are described in detail, including *what amino acids* can occupy *which specific restricted positions* of the sequence motif (*e.g.*, P1, P4, and P6 for PV). Also in each example, the reasons to select those amino acids for each of P1 to P6, *based upon the structures of the respective HLA-DR binding pockets*, are described in detail (see p36-37 for PV, p40-43 for MS).

This leads to the defined PV motif #1 for the only *then known* PV-associated HLA-DR4 allele, DRB1*0402, and the defined MS motifs #1-3 for the only *then known* MS-associated HLA-DR2 allele, DRB1*1501. Using this highly structurally defined PV motif #1, for example, one skilled in the art only needs to search the sequence of a single protein (the known PV autoantigen DG3) 40 times (multiplying **5** possible P1 residues, with **2** possible P4 residues, and **4** possible P6 residues) to obtain the seven polypeptides meeting the structural requirement of the claimed genus. Any polypeptides also meeting the functional requirements of the claims are within the scope of the claimed invention. Thus each of SEQ ID NOs. 1-15, is disclosed species within the genus of closely related claimed polypeptides defined both by *structural* and *functional* similarity.

The disclosed species are also representative of the claimed genus for two reasons. First of all, DRB1*0402 was the only *then known* PV-associated HLA-DR4 allele at the time of filing,

[2] For example, the Rheumatoid Arthritis-associated HLA alleles DRB1*0101, DRB1*0401, and DRB1*0404.

and DRB1*1501 was the only *then known* MS-associated HLA-DR2 allele at the time of filing. Their sequences and binding pocket structures are adequately described in the specification, and the sequences motifs based upon these structures are delineated in detail. Thus any *later identified* PV- or MS-associated HLA alleles, *if any at all*, may yield similar sequences motifs within the scope of the claim. But at least as of the time of filing, Applicants have described not just representative, but almost *all then known* PV- or MS-associated HLA-DR alleles, their binding pocket structures, and the sequence motifs based thereupon, thus meeting the written description requirement. Secondly, using the subject sequence motifs to search other human proteins (not just DG3), or other human pathogen polypeptides is expected to yield additional *structurally and functionally* similar polypeptides within the claimed genus. The disclosed species are representative of these other polypeptides, due to the dual restriction of structural limitations (*e.g.*, fit in the same sequence motifs) and functional limitations (*e.g.*, bind HLA-DR, and stimulate autoreactive T-cells).

Applicants wish to draw the Examiner's attention to the close parallelism between this instant claimed genus and the claimed genus of DNA in Example 9 above.

In Example 9, the hypothetical claim is directed to a genus of nucleic acids, all of which must hybridize with SEQ ID NO: 1, and must encode a protein with a specific activity. Since the hypothetical SEQ ID NO: 1 is novel and fully disclosed, and falls within the scope of the hypothetical claim, the single species meets the written description requirement. As to the genus claim, the Guideline further elaborates that "a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus a representative number of species is disclosed...and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention" (emphasis added). Thus the Guideline concludes: the claimed invention is adequately described.

Example 9 discloses a single species (*e.g.*, SEQ ID NO: 1) within a claimed genus, which encompasses numerous variants (*e.g.*, literally millions, if not tens of millions of sequence variants for a typical 100-nucleotide sequence with merely 3 or less nucleotide changes). Yet, as long as these sequence variants can hybridize under stringent condition with the disclosed single species, and encode proteins with a specific activity, all variants are deemed to have been

adequately described based on the description of SEQ ID NO: 1. This is the case even if there is no generally applicable theory or algorithm in the art (then or now) which would have taught a structure-function relationship adequately, such that a skilled artisan would have been able to determine *a priori*, which variant molecules would have retained the ability to hybridize, and would have retained a useful function as the original protein encoded by SEQ ID NO: 1.

Applicants note that hybridization as exemplified in Example 9 essentially restricts the claim to variants that can actually hybridize with SEQ ID NO: 1, thus ensuring a certain degree of *structural* limitations on all variants within the scope. Applicants also note that requiring the proteins encoded by the variants to retain a biological activity of the parent compound further ensures a certain degree of *functional* limitation on all variants within the scope. This approach, endorsed by the USPTO itself, is sensible, since it protects Applicants against would-be competitors who use routine methods in the art to create numerous minor structural / functional variants of the specific compounds recited.

Applicants submit that the instant claims closely mimic the claims in Example 9. Here, 15 species are described for a much smaller claimed genus, which only encompasses *human* polypeptides or *human* pathogen polypeptides,[3] each must also have at least one of the limited number of sequence motifs. Furthermore, Example 9 defines the structural element by high stringency hybridization, which is impossible to predict without experimentation. In contrast, the instant claimed genus defines the structural element by the presence of definitive sequence motifs. Therefore, the written description requirement is met for the claimed genus.

The Office Action is concerned that only certain motif positions are restricted, while the others "may not be motif amino acids and may actually be deleterious to binding." Applicants submit that the sequence motif is a *structural* limitation of the claimed genus, while ability to bind is one of the *functional* limitations. Any polypeptide meeting the structural requirement but does not bind to the respective HLA-DR protein is outside the scope of the claimed invention.

The Office Action alleges that the specification does not disclose which (other) HLA-DR alleles are known at the time of filing, nor their binding pocket structures, sequence motifs, or core binding residues thereof. Applicants submit that the Office Action refers to the section

[3] Compared to the *millions* of polynucleotide sequences in Example 9, there are only less than 50,000 human proteins, and a viral genome typically encodes no more than 100 proteins.

describing the general approach for defining sequence motifs (see above). The specific HLA-DR alleles associated with the claimed diseases (*e.g.*, DRB1*0402 and DRB1*1501), their binding pockets and sequence motifs are described in the specific examples (see above). Thus the specific DR alleles mentioned in the Office Action, such as DRB1*0401, DRB1*1101, DRB1*1104, DRB1*1301, and DRB1*1302, are not pertinent to the claimed invention. In addition, "large basic residues" are within (and do not contradict) the general class of "hydrophilic residues"; and none of the N, S, T, Q, H, R are the "largest and aromatic residues," which term fittingly describes residues such as W, Y, or F.

The Office Action alleges that no PV-associated HLA-DR4 other than DRB1*0402, and no MS-associated HLA-DR2 other than DRB1*1501 are disclosed in the specification. Applicants submit that these are the only *then known* PV- and MS-associated DR alleles. Applicants have no duty (indeed it is impossible) to describe other PV- or MS-associated DR alleles, if any at all. This is distinguishable from Eli Lilly, where only one species was described when it is known that other unknown species exist. In the instant case, the only known species were described. The other three then known DR2 alleles, such as DRB1*1502, DRB1*1601, and DRB1*1602, are mentioned in page 49.

The Office Action alleges that the specification does not disclose whether polypeptides of SEQ ID NOs. 1, 2, and 5-7 bind DR4, or activates PV patient T-cells. Applicants submit that these specific polypeptides are possible species within the claimed genus. As argued above, any polypeptide meeting the structural requirement but does not bind to the respective HLA-DR protein is outside the scope of the claimed invention. But the mere presence of such candidate species does not render the claimed genus fail to meet the written description requirement.

The same arguments apply to the concern raised by the O'Sullivan reference and the Karin reference. Especially for the latter, Applicants do not understand what is meant "amino acid residues not recited in the claimed 'human' or 'human pathogen' polypeptides will play a pivotal role in determining whether the peptides recited in the claims are capable of being immunogenic, and by extension tolerogenic."

Applicants submit that the subject sequence motif (and the claimed polypeptide) contains the "core MHC binding residues," which means "the residues of an epitope corresponding to the P-1 to P9 positions of an epitope bound to an HLA-DR molecule" (p52, last paragraph, emphasis

added). The specification teaches that MHC binding residues (such as P1, P4, P6, P7, and P9) are *interdigitated* with potential TCR contact residues (such as P-1, P2, P3, P5, P8, and P11). In other words, the sequence motif of the invention inherently and necessarily contains both MHC contact residues and TCR contact residues, due to the linear nature of the polypeptide. The functional requirements of binding to HLA-DR, AND activating T-cell further render it impossible to have a claimed polypeptide not having TCR contact residues. In fact, in Karin, residue 91, the TCR contact residue, is sandwiched between the MHC contact residues 90 and 92-94 (see abstract and Figure 3 of Karin). Figure 2 of the cited Anderton reference is another schematic illustration of such a TCR / polypeptide / MHC complex.

To further illustrate the point, Applicants have listed the fifteen identified peptides (SEQ ID NOs. 1-15) in the table below, indicating which residues are specifically taught by the specification as MHC contact residues (or HLA-DR-binding residues, represented by the subscript "M" and double underline), and which residues are specifically taught by the specification as TCR contact residues, represented by the superscript "T."

Table HLA-DR-Contacting Residues and TCR-contacting Residues for SEQ ID NOs. 1-15

SEQ ID NO.	P-4	P-3	P-2	$P\text{-}1^{T}$	$\underline{P1_{M}}$	$P2^{T}$	$P3^{T}$	$\underline{P4_{M}}$	$P5^{T}$	$\underline{P6_{M}}$	$\underline{P7_{M}}$	$P8^{T}$	$\underline{P9_{M}}$	P10	$P11^{T}$
1	A	T	Q	K	I	T	Y	R	I	S	G	V	G	I	D
2	F	G	I	F	V	V	D	K	N	T	G	D	I	N	I
3	L	N	S	K	I	A	F	K	I	V	S	Q	E	P	A
4	T	P	M	F	L	L	S	R	N	T	G	E	V	R	T
5	C	E	C	N	I	K	V	K	D	V	N	D	N	F	P
6	S	A	R	T	L	N	N	R	Y	T	G	P	Y	T	F
7	Q	S	G	T	M	R	T	R	H	S	T	G	G	T	N
8	F	R	Q	L	V	H	F	V	R	D	F	A	Q	L	L
9	D	F	E	V	V	T	F	L	K	D	V	L	P	E	F
10	D	R	L	L	M	L	F	A	K	D	V	V	S	R	N
11	I	G	G	R	V	H	F	F	K	D	I	S	P	I	A
12	T	G	G	V	Y	H	F	V	K	K	H	V	H	E	S
13	Y	R	N	L	V	W	F	I	K	K	N	T	R	Y	P
14	M	A	R	A	A	F	L	F	K	T	V	G	F	G	G
15	G	G	R	R	L	F	F	V	K	A	H	V	R	E	S

The Office Action also alleges that there is no written description for TCR contact residues in the claimed polypeptide. Applicants submit that the written description requirement does not require Applicants to literally list the exact sequences of TCR contact residues in the claimed polypeptide, just like Example 9 does not list the exact sequences of the millions of variant sequences that end up hybridizing to SEQ ID NO: 1 there. In fact, Example 9 does not list *any* exact sequences other than SEQ ID NO: 1. If the literal languages of Fiers and Amgen are taken out of context, then Example 9 arguably also fails to meet the written description requirement, since it defines the claimed genus of polynucleotides not by the sequences but by "a potential method of isolating it (*e.g.*, high stringency hybridization)." This position clearly would not be consistent with the controlling case law and the PTO policy. Applicants fail to see a qualitative difference between a single fixed sequence (SEQ ID NO: 1) in Example 9, and the defined sequence motifs of the claimed invention.

In fact, for reasons described in pages 18-19, certain TCR contacting sites probably should not be limited in the subject sequence motifs. For example, in the PV example disclosed in the specification, it was previously known that the human desmoglein 3 protein (DG) is the autoantigen, but there was no specific knowledge about which of the many possible epitopes within the DG protein might be causing the autoimmune response. Indeed, the specification has identified several such DG epitopes, each of which, when presented by the PV-associated HLA-DR4, is expected to bind to a different TCR, thus involving different T cell contact residues. This is also confirmed by the fact that two of the seven identified epitopes specifically activate proliferation of autoimmune patient T cells (page 38, last paragraph). In a subsequent article published by the inventors, two additional identified peptides (*i.e.*, SEQ ID NOs. 5 and 7) are shown to react with autoreactive T cells from other PV patients (see page 11937, Table 3 of Wucherpfennig *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**: 11935-39, 1995, submitted as **Exhibit B** in the RCE Submission).

The Office Action also alleges that the specification does not disclose "which amino acid residues or sequences of amino acid residues are associated with a 'human polypeptide,' nor with 'human pathogen polypeptide,... which amino acid residues are associated with 'human pathogen polypeptide' that infect other species as well as humans. ... any 'human pathogen peptide' that is associated with PV, nor any 'isolated human polypeptide' or protein comprising a

subsequence that is an 'isolated human polypeptide' other than those that derive from desmoglein-3 for PV."

Applicants submit that all protein sequences *then known* in the public database PIR and SwissProt were searched, including all *then known* viral and bacteria pathogen proteins (see page 43, last paragraph). Since at the time of filing, it is well-known if a particular matching peptide is from a human pathogen or non-pathogen bacteria or virus, a representative number (if not all) of human pathogen proteins are provided. The patent law does not require Applicants to recite which proteins are *then known* in the public database to satisfy the written description requirement. Whether a human pathogen also infect other species is irrelevant to the written description requirement of the claimed invention.

Similarly, DG3 was the only *then known* human protein associated with PV. Applicants are not obliged to described any other human proteins (if any at all) that might later be found to also cause PV.

In summary, Applicants have provided sufficient functional and structural information for the claimed genus of polypeptides. Applicants have further provided a representative, if not an exhaustive list of species polypeptides within the claimed genus. Therefore, written description requirement is met. Reconsideration and withdrawal of the written description requirement rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph – Enablement

Claims 3-6, 11, 30, and 31 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabling.

Specifically, the Office Action alleges that SEQ ID NOs. 1, 2, and 5-7 are not enabled, since the specification allegedly does not disclose if they are capable of binding to a PV-associated HLA-DR4 or autoreactive T-cells, and if they can be used for tolerization.

The specification describes that the seven DG3 peptides having the PV motif #1 sequence are tested for their ability to bind autoreactive T-cells from two PV patients, and SEQ ID NOs. 3 and 4 are found to be able to do so. However, that does not necessarily mean that SEQ ID NOs. 1, 2, and 5-7 cannot bind other autoreactive T-cells from other PV patients. Other PV patients may have expanded T-cells with specific TCRs recognizing one or more of SEQ ID NOs. 1, 2,

and 5-7. In fact, in a subsequent article published by the inventors, two additional identified peptides are shown to react with autoreactive T cells from other PV patients (see page 11937, Table 3 of Wucherpfennig *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**: 11935-39, 1995, submitted as **Exhibit B** in the RCE submission). This also demonstrates that different patients may have different (subsets of) autoreactive T-cells (*e.g.*, patient 1 may have T cells recognizing PVA.3 and PVA.4; patient 2 may only have T cells recognizing PVA.7, *etc.*), thus a negative result in a limited number of tested patients may not necessarily mean that an identified autoreactive epitope cannot activate any autoreactive T-cell from some (as yet untested) patients. The scope of the claims should not be limited to the Examples provided in the instant specification.

Indeed, four out of seven putative polypeptides meeting the structural requirement of the corresponding new Claim 32, based on a functional assay of a mere four tested patients (see **Exhibit B** submitted in RCE), is an indication that independent Claim 32 is fully enabled. Even if one or more remaining SEQ ID NOs. fails to be recognized by the limited number of tested autoreactive PV T-cells, the independent Claim 32 is still not non-enabled simply because of the presence of certain polypeptides outside the scope of the claim.

The Office Action also alleges that the specification provides no guidance as to what alterations will result in a functional polypeptide (*i.e.*, binds HLA-DR and T-cell), and thus a skilled artisan would have had to engage in undue experimentation to arrive at the functional polypeptides.

Applicants submit that a skilled artisan does not need to know what alterations may be needed to arrive at a functional polypeptide, since the claimed polypeptides are generated based on an approach to screen one or more known proteins (*e.g.*, DG3 or SwissProt database). In fact, four out of seven peptides having the subject sequence motif actually binds autoreactive T-cells from a testing of merely four PV patients, and three out of seven tested MS T-cell clones were activated by several viral / bacterial pathogen polypeptides. Obviously, given the high success rate compared to that in In re Wands, a skilled artisan need not engage in undue experimentation to practice the claimed invention.

The Office Action is also concerned about the possibility of having the PV- or MS-associated HLA-DR protein binding a large polypeptide in a different frame, *e.g.*, the large polypeptide may have more than one binding motif, leading to different sets of possible TCR

contact residues. However, the Office Action does not explain why this allegation, even if true, renders the claimed invention not enabled. Applicants are also unclear why such an "alternative binding frame," presumably also falls within the subject sequence motif, will escape being identified as a possible claimed polypeptide in the first place. Regardless, Applicants submit that different TCR contact residues either allow the polypeptide to bind the autoreactive T-cells (which makes it just another species of the claimed polypeptide), or does not allow the polypeptide to bind the autoreactive T-cells (which makes the polypeptide outside of the scope of the claimed polypeptide). Either way, the corresponding new Claim 32 is still enabled.

The Office Action asserts that Applicants need to make about 1 billion peptides for the screening methods to work. This is based on a misunderstanding of the claimed invention. By fixing the P1, P4, and P6 positions to the 40 limited combinations for PV motif #1 (see above), the skilled artisan does not synthesize 1 billion combinations of polypeptides and test them individually for their ability to bind HLA-DR or activate T-cells, as the Office Action suggests. Instead, according to the teaching of the specification, the skilled artisan performs sequence motif searches first, using known computer programs, against known protein (such as DG3), or public protein databases, such as SwissProt and PIR (see above). Only those peptides matching the structural requirement, *e.g.*, those with required sequence motifs, are obtained for further functional testing. Thus the Office Action has clearly mis-understood the teaching of the specification by omitting a key step for a key structural limitation of the claimed invention.

The Office Action further asserts that "knowledge of the pocket amino acids alone is not sufficient for determination of binding motif." Applicants submit that this assertion is largely rendered moot, in view of the fact that there is only one PV-associated DR4, and one MS-associated DR2 at the time of filing. Furthermore, different DR subtypes are merely polymorphisms of the same gene, and it is expected that they will share very high sequence homology. In fact, page 49 of the specification indicates that the 1601 and 1602 DR2 subtypes differ only by a single amino acid. Thus it is almost certain that many of the binding pockets between different DR2 subtypes (or DR4 subtypes) will be identical or nearly identical. Thus the Office Action assertion that "knowledge of the pocket amino acids alone is not sufficient for determination of binding motif" is not based on sufficient fact finding or scientific reasoning.

The Office Action also asserts, without giving a specific reason, that even PV motif #1 is not fully defined. Applicants respectfully disagree. Not fixing every single position in the PV # 1 motif apparently does not prevent the Applicants to identify seven potential DR4-binding polypeptides, 4 of which have since been verified to activate autoreactive T-cells (see specification and **Exhibit B** in RCE Submission). Such a high success rate supports the notion that the PV # 1 motif is sufficiently defined.

Therefore, Applicants submit that all pending claims are enabled and to the full extent. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 3-6, 11, 30, and 31 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Specifically, Claims 3 (not 1) and 30 are rejected because it is allegedly unclear what the term "consisting of a sequence motif for an HLA-DR protein containing the core MHC binding residues" means. Specifically, the Examiner asked: "(i) if an HLA-DR binding peptide is meant or not, and (ii) if a polypeptide consists of a sequence motif containing the core MHC binding residues, it only contains the core residues and no other."

Applicants are not certain about question (i). But if it can be interpreted as asking whether the polypeptide binds to HLA-DR, Applicants submit that this relates to the *functional* limitation of the claims, and is adequately addressed by the clause "wherein said polypeptide binds to said HLA-DR protein." As used herein, however, the rejected term merely serves to set forth the *structural* limitation of the claimed polypeptides, *e.g.*, the polypeptide must consists of a sequence motif, which is *based upon the structure of the HLA-DR binding pocket*, and the sequence motif contains the core MHC binding residues.

As to question (ii), the sequence motif is one linear sequence, and thus cannot contain just the core MHC binding residues and no others. As argued above, the MHC binding motifs are *interdigitated* with other residues, such as TCR contact residues. See Table 1. A skilled artisan will readily understand the meaning of the claim language when the claim is read in light of the specification. See Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986). Thus Applicants submit that the claim language is not indefinite.

The Office Action also rejected Claims 1 (should be Claim 3) and 30 for improper Markush language. Applicants have use the correct Markush language in the corresponding new claims to obviate this rejection.

The Office Action also rejected Claim 5 because the term "PV motif #1" is allegedly unclear. While not acquiescing in the reasoning of the Office Action, Applicants have inserted the SEQ ID NO. for the claimed PV motif #1 in the corresponding new Claim 34.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Double Patenting Rejections

The Office Action states that Claims 3-6, 11, 30, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 3 and 4 of U.S. Pat. No. 5,874,531.

Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Claim rejections under 35 U.S.C. §102

The Office Action rejects Claim 3 under 35 U.S.C. § 102(a) as allegedly being anticipated by Ohashi *et al.* (*Dev. Neuroscience* **17(3)**: 189, 1995, "Ohashi #1" thereafter); Kondo and Ohashi; Ohashi *et al.* (*J. Neuroimmunology* **54(1-2)**: 186, "Ohashi #2" thereafter).

These three references appear to have originated from the same research group, and appear to refer to the same set of experimental results. Thus at the absence of evidence to the contrary, Applicants will treat them as the same and address them together below.

The Office Action first admits that Ohashi does not teach the peptide in a pharmaceutical preparation, but then the Office Action seems to have relied on the inherent anticipation theory, and alleges that Ohashi anticipates the claimed pharmaceutical composition, because "in order to have determined that the said polypeptide is a T cell epitope, the epitope would necessarily have

been dissolved in a carrier compatible with viability of human T cells, *i.e.*, a pharmaceutically acceptable carrier."

Applicants submit that the Office Action erroneously equates any generic PLP peptide solution[4] with the pharmaceutically acceptable carrier of the corresponding new Claim 32, by assuming that such medium or solution inherently contains the pharmaceutically acceptable carrier of Claim 32. Pursuant to MPEP 2112, "Examiner must provide rationale or evidence tending to show inherency." The same section of MPEP further states that "[t]he fact that a certain results or characteristics may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)," (emphasis in original), and that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)."

Applicants have obtained a copy of Ohashi #2 (submitted herein as **Exhibit A**), the "material and methods" section of which indicates that "split-well" synthesized PLP peptides were used in the experiments. As a skilled artisan would readily understand, such a solution is NOT intended / suitable for *in vivo* use, if directly useable for *in vitro* assays at all. There is neither suggestion nor need to add any "pharmaceutically acceptable carrier" to such a peptide solution for the type of assay described in Ohashi #2. There is also not any indication that such pharmaceutically acceptable carrier was indeed added to the peptide solution used. And there is no evidence whatsoever that any substances potentially harmful for human use were removed from such a peptide solution in order for it to become a claimed pharmaceutical preparation. Thus the Office Action has failed to "establish the inherency of that ... characteristic," and has failed to "provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."

[4] Ohashi #2 discloses that "split-well" synthesized PLP peptides were used in the experiments (**Exhibit A**).

Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**, under **HUIP-P02-001.**

Respectfully Submitted,

Date: August 29, 2005

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P13.12

SYSTEMIC PASSIVE TRANSFER STUDIES (SPTS) IN NEUROPATHY ASSOCIATED WITH ANTIBODIES TO SULFATIDE (SUL).

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Introduction: Anti-SUL antibodies (Abs) used via SPTS as in the Tatum's model (1993) for anti- MAG Abs. **Materials and Methods:**IgM-Lambda paraproteinemia (PP) with anti-SUL Abs from patient with sensory-motor neuropathy (Anti-SUL Titre 1:128.000) and two control IgM-PP were prepared from plasma by Tatum's method (1993). Two-day-old rabbits (N.36) were injected intraperitoneally (IP) with IgM (20 mg/100gm) and one day later they received cyclophosphamide (30mg/100 gm). Rabbit (R) received IP dose of 200 mg at the 1st week (W)(R serum-human IgM :670 mg/dl), 300 mg at the 2nd W,750 mg at the 3rd W . No weight loss or hindlimb paraparesis was observed. **Results:**IgM-Lambda binds to Schmidt-Lanterman incisures, to paranodal myelin at the nodes of Ranvier and to thin nerve fibres in DRG on cryostate sections. Vesiculovacuolar degeneration of the paranodal myelin of sciatic nerve was observed in EM study . **Conclusions:** This model allows to study neuropathy associated with IgM-PP with anti-SUL Abs.

W05.03

A SMALL HEAT SHOCK PROTEIN SERVES AS IMMUNODOMINANT T-CELL ANTIGEN IN MS-AFFECTED HUMAN MYELIN

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The development of antigen-specific intervention in multiple sclerose requires identification of relevant target antigen(s). The aim of our studies was to examine the relative immunogenicity of all CNS myelin proteins to human T cells and to identify possibly immunodominant novel proteins.
For this purpose, peripheral blood T cells from 27 HLA-typed donors, including five definite MS patients, were cultured with total protein extracts from either purified control human myelin or MS-affected human myelin. After 2 weeks, bulk T cells were tested on proliferative responses to all myelin proteins from either source following high-resolution fractionation by reversed phase HPLC. Response profiles of bulk T cell cultures gave virtually identical results for all donors, irrespective of HLA typing or clinical status. All cultures showed marked responses to the HPLC fractions containing minor myelin proteins whereas only modest responses, if any, were detected to either MBP- or PLP-containing fractions. Notably, the protein isolate from MS-affected brain yielded a protein fraction that triggered the highest proliferative response in all cases examined. The protein responsible for this response was identified as a small heat shock protein. Structural characteristics of this protein will be presented as well as immunohistochemical studies on its localization in the human CNS.

W14.05

NEW INSIGHTS INTO THE NEUROPATHOGENESIS OF HIV-1 DISEASE

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Introduction: CNS manifestations of HIV-1 infection result from viral replication in brain macrophages. A comprehensive series of studies towards understanding HIV-1 neuropathogeneesis was initiated.
Materials and Methods: RNA PCR, immunocytochemistry, cytokine bioassays, HPLC, nitrite and neurotoxicity assays were performed in in vitro model systems utilizing primary brain cells and tissue from patients with HIV-1 encephalopathy.
Results: In vitro, HIV-infected monocytes induced expression of E-selectin and VCAM-1 in microvascular endothelial cells, while uninfected monocytes induced only low levels of VCAM-1. In vivo, upregulation of E-selectin and VCAM-1, but not ICAM-1, in microvascular endothelial cells correlated with HIV encephalopathy. LPS treatment of HIV-infected monocytes resulted in overexpression of eicosanoids, PAF, and TNF-α. Human fetal astrocytes down-regulated TNF-α, eicosanoids, and PAF production by HIV-infected monocytes. In contrast to normal monocytes, HIV-infected monocytes produced low levels of NO, that was greatly enhanced after TNF-α stimulation. Expression of iNOS was also detected in pathological brain tissue. PAF placed onto human neurons produced NMDA receptor dependent neurotoxicity. PAF was also identified in CSF of AIDS patients.
Conclusion: Our brain cell models identified "putative" HIV-1 induced neurotoxins including: eicosanoids, PAF, NO and TNF-α. Mechanisms for viral entry and neuropathogenesis in HIV-1 disease were shown that ultimately may lead to better clinical monitoring and treatment strategies.

P16.04

UNRESPONSIVENESS INDUCED IN SENSITIZED MICE IS FRAGILE

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Introduction: Prophylactic tolerance induction to neuroantigens is achievable by a variety of different means. However to be of therapeutic relevance, tolerogenic protocols should be able to modulate established disease.
Materials and Methods: Biozzi AB/H mice were actively sensitized to spinal cord autoantigens using Freund's adjuvant. Depleting and non-depleting CD4-specific monoclonal antibodies (mAb) were injected i.p., or antigen-coupled splenocytes (Ag-SC) injected i.v. at various times following the sensitization process.
Results: Therapeutic administration of CD4-specific mAb can inhibit the development of CREAE, however relapse invariably occurs following cessation of treatment. Relapses can be synchronized by applying antigen rechallenge in adjuvant. These are suppressed if applied under the cover of mAb, yet within 2 weeks from treatment, rechallenge was not prevented. Likewise although prophylactic and therapeutic treatment with Ag-SC during the pre-acute, acute and pre-relapse period could prevent disease development, such hyporesponsiveness could be reversed in sensitized animals by antigen rechallenge.
Conclusions: Naive T cells exhibit a different threshold for tolerance induction than primed cells. Although inhibition of disease can be achieved by a variety of methods, unresponsiveness induced by CD4, CD3 mAb or specific antigen is fragile and can be overcome by the application of an exogenous antigenic stimulus.

W10.02

TCR PEPTIDE-SPECIFIC T CELLS INHIBIT ACTIVATION OF ENCEPHALITOGENIC T CELLS

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TCR peptides, namely Vβ8.2-39-59 or the minimal idiotope, Vβ8-44-54, can treat experimental autoimmune encephalomyelitis (EAE) in Lewis rats, presumably by activating naturally induced TCR peptide-specific T cells that arise in response to the focused appearance of Vβ8.2+ encephalitogenic T cells. The purpose of the present study was to evaluate the mechanisms by which TCR peptides inhibit EAE. Our results indicate that regulation of encephalitogenic T cells is mediated directly by Vβ8.2-39-59 peptide-specific T cells that are induced directly by cell-cell interactions, or even more efficiently, by soluble TCR peptides. This activation of TCR peptide-specific T cells leads to the production and release of soluble factors that locally inhibit the activation of Vβ8.2+ encephalitogenic T cells expressing MHC-bound idiotopes of the target Vβ chain, and possibly "bystander" specificities expressing different Vβ chains. The singular ability of the Vβ8.2-39-59 peptide-specific T cell lines, which are exclusively CD4+ CD8^{lo}, to inhibit activation and EAE transfer, would argue against a role for classical CD8+ T cells in the regulatory circuit. This finding is in contrast to the mouse models of TCR peptide-induced regulation, in which CD8+ T cells are thought to play a critical role.

P06.15

ANALYSIS OF PLP-SPECIFIC T CELLS IN MS: IDENTFICATION OF PLP 95-116 AS HLA-DR2 ASSOCIATED DETERMINANT

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Introduction: In spite of the suggestive role of PLP-specific T cells in the pathogenesis of MS, it remains to be elucidated whether particular PLP determinant (s) would be preferentially recognized by autoimmune T cells in MS.
Materials and Methods: Seven PLP peptides encompassing human PLP85-159 were synthesized. Using the "split-well" method, T cell lines (TCL) were generated against PLP peptides from the blood of Japanese MS and healthy subjects (HS).
Results: Peptide-specific TCL were generated more consistently from MS than from HS ($p<0.001$) as a whole. TCL frequency analysis showed that the frequency of PLP95-116 specific T cells was significantly higher in MS vs. HS ($p=0.036$), and in DR2$^+$ MS vs. DR2$^-$ MS ($P=0.012$).
Conclusion: PLP 95-116 may be encephalitogenic in some DR2$^+$ individuals.